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ABSTRACT

In the kidney, both anions, phosphate and sulfate are almost freely filtered and afterwards reclaimed (reabsorbed) to a large extent from tubular fluid along the proximal tubules. Under normal dietary conditions, fractional excretion of these anions is approximately 10%. Reabsorption of both anions occurs along the proximal tubules by active, saturable and regulated transepithelial processes. Most of the transporters involved in renal handling of phosphate and sulfate have been identified and their transport functions as well as their cellular localizations have been described in detail. The role of these transporters in the renal handling of phosphate and sulfate has been investigated by the use of several mice knock out models and also by analysis of several inherited human diseases. Numerous hormonal and non hormonal factors, have been described that alter renal excretion of phosphate or sulfate by mechanisms that alter the abundance of known phosphate/sulfate transporters and and consequently renal excretion. These mechanisms contribute to the homeostasis of the extracellular concentrations of phosphate and sulfate.

PHOSPHATE

Inorganic phosphate is a nutrient that is essential for many biological processes, such as bioenergetics, metabolic regulation, and for structures such as bones and membranes. In addition, phosphate participates in acid-base balance by contributing to urinary buffering. Approximately 85% of total phosphate is located in bone and teeth, 14 % resides in soft tissues and erythrocytes and only 1% circulates as free phosphate in extracellular fluids.

Dietary intake of phosphate is closely related to the intake of meats, vegetables, and dairy products. As general estimates, milk and milk products contain ~250 to 300 mg of phosphorus per typical serving; meat and fish ~100 -200 mg; vegetables, ~50 -100 mg; and fruits and grain products, 10-50 mg.

The recommended daily dietary allowance for phosphorus is around 800 mg for adults and 1200 mg for children between ages of 11 and 18 years (see http://lpi.oregonstate.edu/infocenter/minerals/phosphorus). A minimum daily requirement is uncertain because negative balance is difficult to achieve in healthy persons. In the absence of abnormalities that affect the gastrointestinal or renal handling of phosphate and/or bone metabolism, the overall output of phosphate adjusts to the intake over a wide range (228).

Organic phosphates ingested in foods are hydrolyzed in the gastrointestinal tract to form inorganic phosphate. Phosphate absorption along the gastrointestinal tract appears to involve two components: i) a transcellular absorptive component, that involves type II and type III Na/Pi-cotransporters (108, 206, 251) and ii) a concentration- or load- dependent absorptive component that may represent paracellular diffusion, that, however, is poorly characterized. The sum of these processes results in an overall fractional absorption of phosphate that ranges between 65% and 70% of the amount ingested (229). Notably, segmental distribution of absorption of phosphate varies among different species. In humans and rats most of the ingested phosphate is absorbed in the upper intestinal segments duodenum and jejunum, whereas in mice, most of the phosphate absorption occurs in the ileum (206, 207, 244). The role of the colon is uncertain.

Overall, control of the extracellular concentration of phosphate depends to a large extent on mechanisms that govern renal excretion of phosphate. Renal excretion of phosphate, and to a lesser extent gastrointestinal absorption of phosphate, is controlled by complex regulatory networks that involve several organs and several endocrine factors (31, 91, 169, 206, 208, 279).

PLASMA PHOSPHATE CONCENTRATION

In plasma, phosphate exists in both the monovalent and the divalent form. Based on the pK-value of 6.8, at blood pH of 7.4, 72 % of plasma phosphate is present in the divalent ($HPO_4^{=}$) and 28 % is present in the monovalent ($H_2PO_4^{-}$) form. In adult humans, total steady-state phosphate concentration in the plasma ranges between 0.8 and 1.2 mM (2.5 to 3.75 mg per deciliter). Different species maintain different normal values for plasma phosphate

concentrations (164). These differences have been correlated with basal metabolic rates. High plasma levels of phosphate occur in mammalian species that exhibit high rates of oxygen consumption and ATP production (267). Plasma phosphate concentrations exhibit diurnal fluctuation due to mechanisms that are not fully understood. In individuals on normal diets, several studies showed consistently that serum concentration of phosphate is highest after midnight and lowest around between morning and midday (205, 238). These diurnal variations are closely matched by a diurnal variation of renal phosphate excretion (37).

Deviations from normal serum phosphate concentrations cause severe clinical disorders. Even slight elevations have been associated with increased rates of death due to cardiovascular complications (292) that are common among patients with chronic kidney disease (136). On the other hand, prolonged hypophosphatemia, caused by e.g. malabsorption or inherited disorders such as X-linked hypophosphatemia (287), results in a number of symptoms such as osteomalacia, hypercalciuria and bone demineralization (7, 153).

METABOLIC REQUIREMENT FOR PHOSPHATE

Inorganic phosphate serves as a cofactor in pathways of energy metabolism such as glycolysis and oxidative phosphorylation. Additionally, phosphate is a cofactor for enzymatic activities involved in a number of metabolic pathways, such as ammoniagenesis or glycogenolysis, and intracellular signaling pathways (36, 42, 43). Moreover, phosphate is required for DNA synthesis and cell replication. Values for intracellular inorganic phosphate concentration/activity are difficult to determine because of the high content and rapid turnover of various organic phosphates. By ^{31}P-NMR, intracellular concentration of phosphate has been estimated to be around 0.7 mM. This value is approximately 30% of values determined chemically (100).

When isolated proximal convoluted tubules are luminally perfused with phosphate-free solution, net sodium transport is eliminated and only partially restored by subsequent perfusion with phosphate-containing fluid. These changes occur inspite of 2 mM phosphate in the bathing medium. Of interest, inhibition of D-glucose transport protects tubular function from limited

phosphate availability (41). These studies indicate that the uptake of luminal phosphate represents a major source for intracellular organic and inorganic phosphates and additionally, that glucose metabolism and mitochondrial respiration compete for a limited pool of available phosphate (41, 42). Similar phenomena have been described in other tissues as “the Crabtree effect”. Limited phosphate availability could impair mitochondrial uptake of substrates whose transport is coupled directly or indirectly to phosphate. Support for this possibility derives from observations that mitochondrial substrates such as succinate, malate, citrate, and glutamate partially restore the transport function of phosphate-limited tubules (117). Alternatively, limited phosphate availability may impair the mitochondrial uptake of calcium or the maintenance of the mitochondrial potential.

RENAL HANDLING OF PHOSPHATE

The overall renal handling of phosphate involves glomerular filtration and tubular reabsorption. There is no evidence for significant secretion of phosphate in kidneys of mammals (115). Phosphate reabsorption displays saturability, but maximal rates vary considerably in response to phosphate intake and levels of different phosphaturic factors. The tubular transport maximum (Tm) for phosphate, therefore, is a variable rather than a constant parameter. As Tm varies with the glomerular filtration rate (GFR), the renal threshold for phosphate (Tm/GFR) should be preferred as a description of the overall renal handling of phosphate. Its normal range lies between 0.77 to 1.4 mMol/L (317). In response to extremes of phosphate intake, the kidneys may excrete close to 100% of the filtered load or as little as none. For individuals in phosphate balance, the daily urinary excretion of phosphate equals the net amount absorbed from the intestinal tract and usually represents 10-20 % of the amount filtered (fractional excretion).

The phosphate concentration in the glomerular ultrafiltrate is determined by the plasma phosphate concentration and the Donnan equilibrium distribution. Measured values of concentrations of phosphate in the ultrafiltrate range between 92 % and 98% of the concentration in plasma water or about 90% of that in total plasma (175). Ultrafilterability declines with increases in plasma calcium concentration in the range between 2.6 mM and 4.6 mM. At very high

plasma calcium concentration ultrafilterability may decrease to about 78% (126).

Localization of Renal Phosphate Reabsorption

Under normal conditions, phosphate reabsorption occurs mainly and essentially only in the proximal tubules. Using free-flow micropuncture techniques, it was observed that the accessible portion of the proximal tubule reabsorbed 76% of the phosphate that was filtered (278). The fraction of filtered phosphate remaining at the end of the proximal tubule (24%) was not different from values measured at the early distal tubule or in the urine indicating that there was no evidence for any net transport of phosphate distal to the accessible proximal tubule when the parathyroid glands were intact. On the other hand, other studies provided evidence for a possible, distal tubular reabsorption of phosphate of approximately 5 to 10% of the filtered phosphate (9). Molecular mechanisms eventually involved in distal tubular reabsorption of phosphate are, however, completely unknown.

Phosphate transport in the proximal tubule displays both axial and internephronal heterogeneity. The latter refers to differences among different populations of nephrons such as superficial versus juxtamedullary. Microperfusion studies of individual proximal tubules demonstrated that phosphate transport rates per unit length did not differ between segments derived from superficial versus juxtameduallary nephrons (210). Therefore, internephron heterogeneity may arise from differences in the lengths or axial composition of superficial and juxtamedullary nephrons. With regard to axial heterogeneity, phosphate reabsorption in the earliest portion, the proximal convoluted tubule (S1), is estimated to be 3 to 4 times higher per unit length compared to the convoluted S2 portion (210, 303). In the proximal straight tubule (S3), rates of phosphate reabsorption are even lower (82). In agreement, higher phosphate transport rates have been demonstrated in brush border membrane vesicles isolated from superficial cortex compared to vesicles isolated from juxtamedullary cortex (180).

CELLULAR MECHANISMS OF PHOSPHATE TRANSPORT

Phosphate reabsorption in the proximal tubule is fundamentally an unidirectional, transcellular process that is strictly dependent on the presence of sodium-ions. A small component of bath-to-lumen flux was reported that may occur via a paracellular pathway. If existing at all, this pathway is not affected by factors that inhibit or enhance phosphate movement from lumen to bath (83, 224, 271).

Phosphate transport across the luminal, apical membrane occurs via sodium-dependent secondary active transport processes that are driven by active extrusion of sodium-ions at the basolateral surface mediated by Na/K-ATPase. Basolaterally located exit transport mechanisms complete transcellular movement of phosphate.

Phosphate Entry

At the apical side of proximal tubular cells phosphate uptake occurs against its own electrochemical gradient. At a negative membrane potential of approximately -60 mV, the free intracellular concentration of phosphate at equilibrium should be roughly 10-times lower than in the extracellular space. However, several measurements indicated that the intracellular concentration of phosphate is around 1 mM and therefore far above the predicted low intracellular concentration of phosphate (100). This suggests that the apical entry of phosphate must be energized. In fact energization is achieved by coupling with sodium-flux that occurs by secondary active sodium-dependent phosphate cotransporters.

Strict dependency of phosphate transport across the apical membrane in proximal tubules on the presence of sodium-ions has been demonstrated in several in vivo (tubules) and in vitro (cells, tubules, purified membranes) assays (83, 296). The major action of sodium-ions is to activate the binding of phosphate to the transport site (312). Sodium dependent transport of phosphate (Na/Pi-cotransport) has been extensively characterized by the use of proximal tubular brush border membrane vesicles isolated from kidneys of different species (83, 224, 296) and by electrophysiological methods using oocytes from Xenopus laevis expressing single Na/Pi-cotransporters (98, 99, 312). Sodium dependence and other characteristics (e.g. pH dependence) of

apical entry of phosphate can be fully explained by the characteristics of cloned Na/Pi-cotransporters.

Na/Pi-cotransporters

Physiologically relevant Na/Pi-cotransporters identified thus far and localized at the apical membrane of proximal tubules belong to the solute carrier families SLC20 and SLC34 (see www.bioparadigms.org/slc/intro.htm) (Figure 1). Some members of the SLC17 family were reported to exhibit Na/Pi-cotransport activity in heterologous expression systems as well, however, it appears unlikely that these transporters play a role in renal handling of phosphate. SLC17a1 (NaPi1) has been cloned based on its (weak) Na/Pi-cotransport activity (324) and has been localized at the brush border membrane of proximal tubules (64). Its role in renal phosphate handling is rather unlikely as neither PTH nor dietary phosphate regulate NaPi1 protein abundance (224). Furthermore, after expression in oocytes of Xenopus laevis, detailed analysis suggested that NaPi1 is transporting various organic anions (47, 246). Moreover, as demonstrated with purified and reconstituted NaPi1 protein, NaPi1 may act as a voltage and chloride dependent urate exporter in proximal tubules (135). As a single nucleotide polymorphism in SLC17A1 has been associated with gout (80), thus urate transport by NaPi1 could be of particular importance in the development of this disease. Another member of the SLC17 family, SLC17A3, was also shown to be localized at the brush border of proximal tubules (139). After expression of SLC17A3 in Xenopus oocytes, transport of phosphate could be demonstrated that was dependent on the presence of sodium-ions. However, the role of SLC17A3 in renal handling of phosphate is not clear. Rather, SLC17a3 appears to be an anion efflux transporter for urate and loop diuretics (145).

The two members of the SCL20 family [SLC20a1 (PiT1) & SLC20a2 (PiT2)] were originally identified as retroviral receptors and later on demonstrated to exhibit Na/Pi-cotransport activity (61, 148). In kidney, PiT2 was localized at the brush border membrane in proximal tubules (309). In rat kidney PiT2 was detected in S1 and to a lesser degree in S2 segments (236). The localization of the PiT1 protein remains to be determined. Na/Pi-cotransport by PiT proteins is electrogenic due to a stochiometry of $2Na^+$ to $1HPO_4^-$ (98, 245).

PiT transporters do not transport sulfate, but interaction with arsenate has been demonstrated (245, 312). The role of PiT2 in proximal tubular reabsorption of phosphate under normal physiological conditions was suggested to be marginal (310). Na/Pi-cotransport activity of PiT transporters is higher at more acidic pH-values (245, 310), therefore PiT mediated phosphate reabsorption may be of primary importance under pathological conditions (e.g. acidotic conditions). The precise role of PiT2 in overall renal handling of phosphate and its regulation remains to be determined.

Both, NaPi-IIa (SLC34A1) and NaPi-IIc (SLC34A3) have been localized at the luminal membrane of proximal tubules (98, 224, 236, 315). Abundance of NaPi-IIa is highest in S1 segments and decreases towards S3 segments. NaPi-IIc has been localized only in the S1 segment (236). Transport kinetics of both isoforms have been extensively studied after heterologous expression in oocytes of Xenopus laevis (98, 99). A fundamental difference between NaPi-IIa and NaPi-IIc lies in the coupling to Na^+-ions. Whereas 3 Na^+ ions are transported together with one divalent phosphate ion (HPO_4^{2-}) by NaPi-IIa, only 2 Na^+-ions are transported with one HPO_4^{2-} -ion by NaPi-IIc. Thus, Na/Pi-cotransport by NaPi-IIa is an electrogenic process, whereas Na/Pi-cotransport by NaPi-IIc is an electroneutral process. Both cotransporters show similar pH dependence with higher rates at more alkaline pH-values (315).

The roles of NaPi-IIa and NaPi-IIc cotransporters in proximal reabsorption of phosphate can be deduced from several observations made with different knock out mouse models and from observations made with several genetic diseases in humans (216). In mice, the important role of NaPi-IIa has been documented by knocking out the Npt2 gene (19, 288). These mice are hypophosphatemic due to phosphate wasting that can be explained by an approximately 70% reduced Na/Pi-cotransport rate in isolated brush border membranes. In humans, the role of NaPi-IIa has been documented less well. Although genetic variants within the NPT2a gene are often observed, these polymorphisms could not be conclusively linked to renal phosphate anomalies (165). On the other hand, an in-frame duplication of a stretch of seven amino acids has been reported in two siblings of a family with hypophosphatemic rickets (190). Renal wasting of phosphate in these patients is associated with Fanconi's syndrome, suggesting that either the duplication of the described

amino acid motif in NaPi-IIa proteins may also affect other proximal tubular transporters as well, e.g. by interfering with sorting or that the genetic defect lies in another gene not identified yet.

In contrast to NaPi-IIa, ablation of the NaPi-IIc cotransporter did not impair homeostasis of phosphate nor was renal reabsorption of phosphate affected in adult mice (264). These observations suggested that, in adult mice, NaPi-IIc plays a minor role in overall renal handling of phosphate. However, opposite to mice, in patients with hereditary hypophosphatemic rickets with hypercalciuria (HHRH, OMIM #241530) mutations within the NaPi-IIc gene have been described that explain the renal wasting of phosphate in these patients (7, 28, 185, 240). Altogether, current findings suggest that NaPi-IIa and NaPi-IIc Na/Pi-cotransporters represent the major players in renal handling of phosphate but may contribute differently in different species.

Phosphate Exit

The molecular identity of phosphate transport across the basolateral membrane is currently not known. Based on basolateral membrane preparations, several transport mechanisms have been proposed. However, because purified basolateral membrane fractions are relatively undefined, it has remained difficult to demonstrate that the transport phenomenon does not represent contamination from other membranes, especially mitochondrial or brush border material.

Uptake of phosphate into basolateral membrane vesicles from dog kidney demonstrated features different from uptake in brush border membrane vesicles. Although sodium-dependency has been demonstrated, uptake into basolateral membrane preparations lacked pH-sensitivity (261). Even if present in basolateral membranes in vivo, an electrogenic, sodium gradient-dependent transport mechanism would favour a basolateral entry – rather than exit- of phosphate, and thus such a mechanism is difficult to integrate into models of net transcellular transport of phosphate. However, it has been proposed that such a mechanism could be involved in protecting the proximal tubule from limited availability of intraluminal phosphate (262).

Other investigations suggested an anion-exchange mechanism based on the observation that preloading basolateral vesicles with phosphate stimulated

phosphate uptake in the absence of sodium (119, 187). For an anion-exchange mechanism to achieve net exit of phosphate, some other counter-ion must be exchanged. The identity of such a counter-ion is not known. Experimental evidence was provided that the phosphate exchange mechanism is distinct from the basolateral sulfate exchange mechanism (116, 119, 188).

REGULATION OF PHOSPHATE EXCRETION

Excretion of phosphate is tightly controlled and adjusted to the metabolic needs by a long list of hormones and metabolic factors which primarily affect the abundance of Na/Pi-cotransporters residing in proximal tubular brush border membranes and therefore net rate of reabsorption of phosphate. These factors are integrated into complex regulatory networks that acutely and chronically regulate renal phosphate reabsorption. These networks comprise different organs such as bone, small intestine, and parathyroid glands (6, 31, 34, 83, 160, 208, 279).

Parathyroid Hormone

Parathyroid hormone (PTH) primarily regulates calcium homeostasis but in addition regulates serum phosphate levels by controlling proximal tubular phosphate reabsorption (107). Acute administration of PTH causes an increase of phosphate excretion within minutes that lasts for several hours (35, 98). PTH has the potential to reduce phosphate transport along the entire proximal tubule. The action of PTH in different proximal tubular segments may be influenced by excessive or restricted dietary phosphate availability (112). In addition, PTH also inhibits proximal reabsorption of sodium and bicarbonate by inhibition of the amiloride sensitive sodium-proton exchanger NHE3 (5) and stimulates production of 1, 25-dihydroxyvitamin D_3 (88).

In proximal tubules, PTH exerts its effect via the PTH receptor PTHR1, which is localized at the basolateral as well as at the luminal membrane. Apical PTHR1 is coupled to Gq and activates a PLC/IP_3/Ca^{2+}/PKC pathway, while basolateral PTHR1 is coupled to Gsα and activates a cAMP/PKA pathway (293). Activation of both PTHR1 pools results in increased excretion of

phosphate due to a decrease of the abundance of apical Na/Pi-cotransporters. In-vivo studies using different PTH analogs demonstrated that down-regulation of the Na/Pi-cotransporter NaPI-IIa (see below) occurs primarily via the cAMP/PKA pathway (225)

PTH provokes a decrease of Na/Pi-cotransporters NaPi-IIa and NaPi-IIc, yet by different mechanisms and time courses (209, 236, 265, 266). After intravenous injection of PTH, a decrease of apical abundance of NaPi-IIa proteins is detectable after 15 min and persists for several hours, while a decrease of the abundance of NaPi-IIc proteins was detected only after more than two hours. Also the abundance and activity of PiT2 is regulated by PTH but the mechanism may be different since no internalization of PiT2 transporters could be detected by immunohistochemistry (236).

Within minutes, PTH leads to an internalization of NaPi-IIa that occurs at the intermicrovillar clefts via clathrin coated vesicles. There is no evidence for a recycling of internalized NaPi-IIa proteins; neither there is evidence for a intracellular pool from which NaPi-IIa proteins could be recruited. After endocytosis, NaPi-IIa proteins colocalize with early endosomes from where they are sorted and trafficked to lysosomes and degraded (98, 151, 236). In contrast, NaPi-IIc proteins have not been detected in a lysosomal fraction after PTH treatment, although the abundance in the brush border membrane was decreased with a delay of several hours (265). The exact mechanism involved in the down-regulation of the amount of NaPi-IIc proteins by PTH remains to be determined.

NaPi-IIa was demonstrated to interact with several proteins. Among those, the PDZ domain containing proteins NHERF1 (sodium-proton exchanger regulatory factor 1) and NHERF3 (PDZK1) showed most robust interactions in in-vitro assays (110, 129). These interactions occur via the most C-terminal amino acids (TRL) of NaPi-IIa. NHERF1 contains two PDZ domains, of which the first one interacts with NaPi-IIa (110, 129) and a MERM (merlin-ezrin-radixin-moesin) binding domain that, via ezrin, links NHERF1 to the β-actin cytoskeleton. As demonstrated with NHERF1 knock out mice, NHERF1 is instrumental for stabilizing NaPi-IIa proteins at the apical membrane (63, 268). In these mice, the apical abundance of NaPi-IIa proteins was reduced resulting in increased urinary phosphate excretion. Reduced abundance of

NaPi-IIa proteins at the apical membrane was associated with accumulation in intracellular structures indicating an impaired targeting of NaPi-IIa proteins to the apical membrane. Furthermore, NHERF1 plays an important role in PTH stimulated endocytosis of NaPi-IIa. The affinity of NHERF1/NaPi-IIa interaction is decreased by phosphorylation of a serine residue (ser77) that is located within the first PDZ domain of NHERF1 by either signalling cascade (PKA, PKC) activated by PTH (322). Consequently, increased mobility of NaPi-IIa allocates NaPi-IIa for endocytosis (323).

In addition to NaPi-IIa, NHERF1 also interacts with PTH receptor PTHR1 and phospholipase C (191). In agreement, apical PTH signaling, but not basolateral signaling was shown to be impaired in NHERF1 deficient mice (49).

In addition to NHERF1, NaPi-IIa strongly interacts with the four PDZ domain containing protein NHERF3 (PDZK1, Cap1) (129) that has been localized at the proximal tubular brush borders as well. However, PDZK$^{-/-}$ mice, exhibit a mild phosphaturic phenotype only under high phosphate diets (50). Besides NaPi-IIa, NaPi-IIc was shown to interact with NHERF3 (PDZK1) as well (308). Functional significance of this interaction was observed in PDZK1 $^{-/-}$ mice fed chronically with low phosphate diet. Compared to wild type mice, up-regulation of NaPi-IIc in PDZK1 $^{-/-}$ was impaired while up-regulation of NaPi-IIa was normal (109). These studies suggest that NHERF3 is involved in the slow adaptive response of NaPi-IIc to low phosphate diet and does not play a role in the fast adaptive response of NaPi-IIa.

Moreover, the epithelial form of shank2 has been shown to interact with NaPi-IIa as well. Microscopic analysis provided evidence that apically localized shank2 cotrafficks together with NaPi-IIa under conditions that lead to a down-regulation of NaPi-IIa proteins, such as during acutely given high phosphate diet (86).

Phosphatonins/Klotho

In recent years, several new phosphaturic factors, now collectively named as phosphatonins, have been identified that contribute to the maintenance of phosphate homeostasis. Originally, the term phosphatonin has been coined to describe circulating phosphaturic factors that are elevated in several diseases,

such as oncogenic osteomalacia (OOM), autosomal dominant hypophosphatemic rickets (ADHR), and X-linked hypophosphatemic rickets (XLHR) (31, 160). These diseases are characterized by hyperphosphaturia, hypophosphatemia, and inappropriately normal or low levels of 1,25-dihydroxyvitamin D_3. To date, the following phosphatonins have been identified: fibroblast growth factor 23 (FGF23), secreted frizzled related protein 4 (sFRP4) and matrix extracellular phosphoprotein (MEPE) (2, 31, 325). The attribution of fibroblast growth factor 7 (FGF-7) is controversial since no phosphaturic effects in vivo could be detected.

FGF23, is primarily produced and secreted by osteocytes and osteoblasts (92). Small levels of mRNA were detected in other tissues such as liver, parathyroid glands, and small intestine (2). The uncleaved, biologically active form of FGF23, consists of 215 amino acids. Cleavage and inactivation of FGF23 occurs at a subtilisin-like proprotein convertase site at position 176 (R176XXR). Mutations at these positions have been associated with ADHR due to reduced cleavage and consequently increased levels of FGF23 (13, 270). Proteolytic cleavage may also be influenced by altered O-glycosylation of FGF23 by UDP-N-acetyl-α-D-glactosamine: polypeptide N-acetyl-glactosaminyltransferase (GALNT3) that has been associated with familial tumoral calcinosis (274).
FGF23 has emerged as the possibly most important regulator of phosphate homeostasis, although, compared to PTH secretion, changes of serum concentrations of FGF23 occur more slowly. Synthesis and secretion of FGF23 is stimulated by dietary phosphate (46, 95, 231, 235,) and 1,25-dihydroxyvitamin D_3 (154). As a feedback mechanism, FGF23 inhibits the production of 1,25$(OH)_2$ vitamin D_3 via inhibition of 1α-hydroxylase activity and increase of 24-hydroxylase activity (183). FGF23 also suppresses synthesis and release of PTH from parathyroid glands (272).

Several in-vivo and in-vitro investigations documented that the phosphaturic effect of FGF23 can be explained by alterations of the apical abundances of proximal tubular Na/Pi-cotransporters. Phosphaturia in FGF23 transgenic

mice correlates with reduced amounts of both NaPi-IIa and NaPi-IIc (166) and overexpression of FGF23 and in-vitro treatment of isolated proximal tubules affected abundances of proximal tubular apical Na/Pi-cotransporters NaPi-IIa, NaPi-IIc and PiT2 (17, 258, 291). FGF23 null mice exhibit severe hyperphosphatemia and have elevated serum levels of 1,25-dihydroxyvitamin D_3 (269).

The phosphaturic effect of FGF23 is mediated via the canonical FGF receptor FGFR1c and requires the membranous form of Klotho as cofactor (106, 306). Cellular signaling elicited by this receptor complex was described to occur via the MAPK kinase pathway (90, 91, 326). The exact signaling cascade regulating Na/Pi-cotransporters by FGF23 remains to be determined. In kidney, Klotho is expressed mainly in distal tubules (90). Injection of FGF23 was shown to induce phosphorylation of MAPK in distal tubules in parallel to a reduction of NaPi-IIa protein in proximal tubules, indicating that an unknown paracrine mechanism could be involved in the action of FGF23 on proximal tubular Na/Pi-cotransporters (90). However, low expression of klotho was demonstrated in proximal tubules as well (134) and therefore may suggest that klotho acts also in an autocrine manner in proximal tubules.

Klotho protein is composed of two extracellular domains that show similarity to β-glycosidases, thus, alternatively to its FGF receptor cofactor function, Klotho may modify transporter function directly via hydrolysis of sugar residues. Evidence for such action of Klotho has been provided in in-vitro experiments. Incubation of isolated proximal tubular brush border membranes with recombinant Klotho protein leads to an inhibition of Na/Pi-cotransport (134).

Frizzled-related protein 4 is overexpressed in OOM tumors (30, 31). sFRP-4 elicits an increase of phosphate excretion that is caused by a decrease of Na/Pi-cotransporter NaPi-IIa abundance (29, 30). sFRP-4 was shown to alter phosphorylation of beta-catenin pointing to a mechanism involving the Wnt-signalling pathway up-stream to a down-regulation of NaPi-IIa (29).

MEPE and FGF7 were identified from tumor tissues of patients exhibiting renal phosphate wasting (31). MEPE, a member of the SIBLING (short integrin-binding ligand interacting glycoprotein) protein family, is primarily expressed in bone cells. The phosphaturic action of MEPE is paralled by a decrease of apical NaPi-IIa protein abundance (85). In cell culture studies,

FGF7 inhibits Na/Pi-cotransport (53). Cellular mechanisms involved in the phosphaturic action of MEPE and possibly FGF7 are not known.

Catecholamines

Nerve endings in proximity to renal tubules release norepinephrine, which acts on proximal tubule to increase sodium, phosphate, and bicarbonate reabsorption (18). These effects are explained by a stimulatory action of norepinephrine on the sodium/potassium pump, as evidenced by norepinephrine induced increases in transport related oxygen consumption and ATP hydrolysis. The effect of epinephrine on renal phosphate handling may be indirect via stimulation of PTH secretion (96).

In kidney, dopamine is synthesized primarily in proximal tubules (274 and its production is regulated by dietary intake of phosphate via stimulation of DOPA decarboxylase activity (321). A number of studies showed that dopamine is both natriuretic and phosphaturic due to autocrine/paracrine actions (105, 111). The phosphaturic effect of dopamine has been demonstrated in several animal models and cultured renal cells (78, 137, 140, 167). Administration of dopamine or its precursors elicit reduced Na/Pi-cotransport at the brush border membrane (84, 137) that is explained by internalization of NaPi-IIa cotranporters (11).

Differential inhibition of D1 and D2 receptors indicated that stimulation of apically localized D1 receptors, via a cAMP/PKA pathway, increase the rate of internalization of NaPi-IIa (11, 62). Similar as for PTH mediated internalization of NaPi-IIa, NHERF1 plays a key role in dopamine induced internalization of NaPi-IIa. The signaling cascade activated by dopamine leads to phosphorylation of Ser77 within a PDZ domain of NHERF1 resulting in a decreased affinity for NaPi-IIa (320).

Atrial Natriuretic Peptide/NO

Atrial natriuretic factors represent a series of peptides that besides vascular actions also have direct effect on proximal tubular functions. Early studies demonstrated that ANP causes phosphaturia associated with a decrease of brush border membrane Na/Pi-cotransport (330). Nitric oxide (NO) was

shown to regulate proximal tubular transport by autocrine/paracrine mechanisms (155).

Guanylate cyclase is activated by both ANP and NO (319). In mice and cultured renal cells administration of ANP and NO donors resulted in a decrease of NaPi-IIa cotransporters. These effects could be mimicked by pharmacological activation of protein kinase G by 8Br-cGMP and inhibited by protein kinase G inhibitors. In-vitro perfusion of isolated proximal tubules suggested the presence of ANP receptors at both membrane sites (12). At this time the target for activated PKG is not known.

Growth Hormone

Growth hormone (directly or indirectly mediated by insulin-like growth factor I) acts on renal proximal tubule to increase phosphate reabsorption (54, 122, 124). Receptors for IGF likely reside in the basolateral membrane (124). In juvenile rats suppression of growth hormone reduced reabsorption of phosphate and abundance of the NaPi-IIa cotransporter to a similar level as observed in adult rats (326). These observations suggest that growth hormone plays an important role in up-regulated phosphate reabsorption in young animals which likely is due to higher anabolic needs.

Insulin/Glucagon

Insulin infusions coupled with sufficient glucose to maintain euglycemia increase renal reabsorption of phosphate in humans (79). Renal cortical tubules display specific binding of insulin, and insulin added to proximal tubules in vitro increases Na/Pi-cotransport in brush border membrane vesicles derived from these tubules (123). At this time, no further information about the cellular mechanisms of insulin action are known. A pathway including the serine/threonine kinase mTOR could be envisaged as insulin represents a stimulator of mTOR. Accordingly, it has been shown that rapamycin, an inhibitor of mTOR, resulted in phosphaturia (149). Furthermore, insulin was proposed to have a role in the adaptive response of renal handling to low Pi-diet. In rats with streptozotocin-induced diabetes, no increase of Na/Pi-cotransport in isolated brush border membranes was detected after low

Pi-diet given for three days (1). Interestingly, at the whole kidney level the adaptive response was normal.
Glucagon may have direct actions on the kidney to enhance calcium and magnesium reabsorption, probably in the thick ascending limb of Henle, but any effects on phosphate excretion are probably indirect (14).

Glucocorticoids

Glucocorticoids, like dexamethasone, triamcinolone, and hydrocortisone increase phosphate excretion by inhibition of brush border Na/Pi-cotransport (184). Independent from the presence of PTH, pharmacologic doses result in decreased phosphate reabsorption within 1-2 h (103). There is special interest in the relationship between glucocorticoids and phosphate transport because glucocorticoids participate importantly in the renal response to metabolic acidosis, including phosphaturia (40, 102) and chronic treatment with glucocorticoids leads to loss of bone mass.
Work performed with cultured renal cells provided evidence for a genomic as well as for a non-genomic mechanism of glucocorticoid-induced phosphate excretion. The latter may be mediated by PKC rather than PKA (232, 313).

Calcitonin

Low doses of calcitonin reduce the fractional excretion of calcium and magnesium but have no effect on phosphate excretion; much higher dosage of calcitonin is required to increase phosphate excretion (52). This suggests that the physiological role of calcitonin is to cause renal conservation of calcium and magnesium, and that increased excretion of phosphate may represent a pharmacological effect. Nevertheless, acute administration of calcitonin increases phosphate excretion. Micropunture studies indicated that calcitonin induced inhibition of phosphate reabsorption occurs in proximal tubules independent of an increase of cAMP (33). Additionally, after a few hours, injection of calcitonin provoked decreased Na/Pi-cotransport in rat renal brush border membranes (329). Curiously, calcitonin has no demonstrable effect on adenylate cyclase activity in the proximal tubule (55).

Thyroid Hormone

Excess thyroid hormone is associated with hyperphosphatemia and increased renal reabsorption of phosphate that is due to altered Na/Pi-cotransport (328). In addition, thyroxine stimulates Na/K-ATPase activity providing increased driving force for Na/Pi-cotransport. Vice versa, the absence of thyroid hormones results in a decrease of of NaPi-IIa protein abundance (4, 259) and increased renal loss of phosphate (217).

Estrogen

Estrogen replacement therapy during menopause results in decreased plasma levels of Pi that has been associated with inhibition of renal phosphate reabsorption (276, 295). In a study using ovarectomized rats, inhibition of Na/Pi-cotransport was observed after treatment with β-estradiol compared to untreated rats (23). Inhibition of proximal tubular transport of phosphate by estrogen has been associated with a specific decrease of both NaPi-IIa mRNA and protein (89) whereas abundance of NaPi-IIc was not altered. Furthermore, no changes of Klotho and NHERF1 mRNA contents have been detected. Although estrogen receptors are expressed in proximal tubules (68), a blocker of the α- receptor did not prevent down-regulation of NaPi-IIa; a possible involvement of the β-receptor has not been investigated. Also, it remains to be tested if down-regulation of NaPi-IIa is directly mediated by estrogen or indirectly, e.g. by a stimulation of the production of dopamine.

Stanniocalcins

The polypeptide hormone stanniocalcin 1 (STE1) and the related STE2 are suggested to be involved in the homeostasis of calcium and phosphate (314). Human stanniocalcin 1 reduced phosphate excretion in rats due to a stimulation of brush border Na/Pi-cotransport (314, 316). No direct effect of STE2 in vivo has been examined. In cell culture, a long term inhibitory effect of STE2 on Na/Pi-cotransport was observed that is likely due to an inhibition of the NaPi-IIa promoter activity (138).

STE1 and STE2 are expressed in several tissues (138). In kidney, expression of STE1 has been repeatedly shown in distal tubular segments, whereas proximal tubular expression of STE1 remains controversial. Available data

therefore suggest that STE1 may act as a paracrine modulator of renal phosphate handling. Renal localization of STE2 is not known (138). Interestingly, expression of STE1 and STE2 mRNA is stimulated by 1,25-dihydroxy-vitamin$_3$ and STE2 mRNA is acutely decreased by PTH (132, 281).

Calcium/Magnesium

It is not possible to provide simple answers to questions about the effects of calcium on phosphate excretion (271). When considering individual studies, one should question the following features: i) Is PTH present or absent? Or, can the observed effects of calcium on phosphate excretion be correlated with corresponding changes in PTH concentrations? ii) Are changes in calcium developing acutely (intravenously over minutes or hours) or chronically (over more than 24 hours)? iii) What are the other specific details regarding changes in calcium concentrations? For instance, are calcium values increased from low to normal, or normal to high, in vivo or in vitro?

Direct tubular effects of calcium on phosphate transport have been studied by various approaches. In isolated tubules from rabbit, increasing the calcium concentration in both bath and the lumen caused progressive increases in phosphate absorption without affecting net sodium transport (250). In vivo microperfusion studies in parathyroidectomized rats demonstrated a decrease in proximal phosphate transport when calcium was omitted from the peritubular and intraluminal fluids, yet changes from 1.5 to 3 mM had no effect (304).

In normal rats fed high magnesium diet, reabsorption of phosphate was increased due to increased abundances of NaPi-lIa and NaPi-lIc (290). This effect has been correlated with a decrease of PTH concentration. Parathyroidectomy abolished the effects of high magnesium diets on NaPi-IIa whereas the effect on NaPi-lIc was not affected, suggesting a PTH independent effect of high Magnesium diet on NaPi-lIc.

Hypokalemia/Potassium Deficiency

Besides impairment of systemic functions, hypokalemia/potassium deficiency provokes morphological changes and affects a number of renal functions including transport rates and metabolic processes. Hypokalemia/ potassium

deficiency leads to hypophosphatemia due to an increase of urinary phosphate excretion (141, 142, 263) that was associated with decreased phosphate transport in isolated proximal tubular brush border membranes (45, 331). Of interest, abundances of Na/Pi-cotransporters are differentially affected by potassium deficiency. While abundances of both NaPi-IIc and PiT-2 were decreased, abundance of NaPi-IIa was increased (45). In addition, lipid composition and membrane fluidity was altered as well. Changes of the contents of sphingomyelin and glucosylceramide were reported to decrease membrane fluidity.

In contrast to potassium deficiency, potassium loading was shown to decrease urinary excretion of phosphate. Stimulation of total renal reabsorption of phosphate by potassium loading was shown to be dependent on intact parathyroid glands. Interestingly stimulation of total renal reabsorption of phosphate induced by intravenous injection of potassium has been associated with an increase of distal tubular reabsorption of phosphate (141).. In control animals no evidence for distal reabsorption was obtained.

Metabolic Acidosis

The increase in phosphate excretion that occurs with metabolic acidosis has at least two physiological roles. First, it provides urinary buffer to enhance the excretion of acids. Second, it reduces the extracellular burden of phosphate that occurs from mobilization of bone mineral (176). Chronic metabolic acidosis in humans causes negative calcium and phosphate balance that results from mobilization of bone mineral (176).

Phosphaturia occurs with metabolic acidosis induced by ammonium chloride, hydrochloric acid, or lactic acid, and is completely reversed by correction of acidemia (118). Interestingly, there is no consistent change in serum phosphate concentration. Thus the major factor that induces phosphaturia appears to be acidemia. The effects of metabolic acidosis on phosphate excretion occur in the absence of PTH (118).

Sensitivity to luminal pH-values of Na/Pi-cotransporters localized at the proximal tubular brush border membranes may explain part of the phosphaturic response elicited by metabolic acidosis. In brush border

membrane vesicles Na/Pi cotransport activity is very sensitive to pH with acidic pH decreasing transport activity (10). The function of both, NaPi-IIa and NaPi-IIc is decreased by an increase of extracellular proton concentration (98). Part of this inhibition is related to allosteric changes in the phosphate transporters, which inhibit sodium activation (312). In addition to the direct and immediate effects of pH on phosphate transporters, acidemia over time eventually reduces phosphate transport by mechanisms related to glucocorticoids that have been shown to reduce phosphate reabsorption (102, 318) or to elevated levels of FGF-23 (158)

Regulation of proximal tubular Na/Pi-cotransporters by metabolic acidosis has been studied in rats and mice. Studies in rats revealed a decrease of NaPi-IIa mRNA that was paralleled by a decrease of the amount of NaPi-IIa proteins (8). In another study in rats kept on a low or normal phosphate diet, acidosis induced phosphaturia only in animals on normal phosphate intake and no decrease in NaPi-IIa, NaPi-IIc or PiT2 expression was found in rats on low phosphate diet (310). Similarly, in mice, metabolic acidosis provoked a decrease of NaPi-IIc and NaPi-IIa mRNA expression, however, protein content of both Na/Pi-cotransporters was increased (230). Thus, at least in mice, metabolic acidosis induced phosphaturia cannot be explained by a down-regulation of type II Na/Pi-cotransporters.

1,25-Dihydroxyvitamin D_3

The active form of vitamin D, 1, 25-dihydroxyvitamin D_3 (1, 25-$(OH)_2D_3$), is primarily formed in kidney proximal tubules by 1α-hydroxlases that are located in the inner mitochondrial membrane. The net serum concentration of 1,25-dihydroxyvitamin D_3 is determined by complex regulations of the 1α-hydroxylase as well as 24-hydroxylase by PTH, FGF23 and dietary phosphate (88, 183). Under normal conditions 1,25-dihydroxyvitamin D_3 appears to have no demonstratable effects on renal handling of phosphate, but rather on intestinal absorption of phosphate (207). A phosphaturic action of 1, 25-$(OH)_2D_3$ appears to be more indirect as increased levels of 1,25-$(OH)_2D_3$ stimulate release of FGF23 from bone that in turn inhibits reabsorption of phosphate. By using 1,25-$(OH)_2D_3$ deficient rats, administration of 1,25-

$(OH)_2D_3$ was shown to increase NaPi-IIa abundance, likely occurring via a transcriptional mechanism (282).

Reduced dietary intake of phosphate increases 1α-hydroxylase activity in proximal tubules and serum concentration of 1,25-$(OH)_2D_3$ (332). In animal models, increase of both activity and mRNA content of 1α-hydroxyalse was delayed by approximately 24 h after the onset of reduced dietary intake of phosphate. In hypophysectomized animals this increase was blunted and therefore appears to be dependent on growth hormones (285). The late onset of 1,25-$(OH)_2D_3$ production induced by low Pi-diet makes it unlikely that 1,25-$(OH)_2D_3$ is involved in the rapid adaptive response to low Pi-diet. In agreement, an intact acute adaptive response of renal Na/Pi-cotransport has been demonstrated in 1α-hydroxylase knock out mice (51).

Dietary Intake of Phosphate

Renal reabsorptive capacity for phosphate varies and adapts profoundly in response to dietary intake of phosphate (289, 303). Phosphate restriction enhances and high phosphate diets reduce the intrinsic capacity of the kidney to reabsorb phosphate. It is useful to distinguish between phosphate restriction (short term) and phosphate depletion (over a long period of time). Renal adaptation to altered intake of dietary phosphate occurs rapidly -within hours- and specifically alters the rate of proximal tubular Na/Pi-cotransport (177, 181, 249). Phosphate depletion represents a more severe state that requires 2-4 weeks of phosphate deprivation and is associated with impaired energy metabolism and multiple reabsorptive defects along the nephron, including those for glucose, amino acids, bicarbonate, and calcium (156). In contrast to reduced intake of phosphate by dietary content of phosphate, fasting provoked only minor changes of renal excretion of phosphate and Na/Pi-cotransport actitvity in brush border membrane vesicles (150).

The proximal tubule is the major nephron site at which adaptation to phosphate restriction occurs. Both early and late portions of the proximal tubule from both superficial and juxtamedullary nephrons are involved in adaptative changes (125). The effect of dietary adaptation on Na/Pi-cotransport has been demonstrated both in isolated proximal tubules (303) and isolated brush border membrane vesicles and is manifested by an

increase in V_{max} without changes in K_m-value (58, 59, 277). Rapid (two hours) adaptation to phosphate restriction leads to increased Na/Pi-cotransport in rat brush border vesicles due to an increase of NaPi-IIa abundance (186, 249). Similarly, rapid down-regulation of Na/Pi-cotransport and abundance of NaPi-IIa protein is observed after intake of excessive phosphate (186, 249). As observed after PTH injection, acute down-regulation of NaPi-IIa protein induced by high Pi-diet involves endocytosis and lysosomal degradation of NaPi-IIa proteins (151).

Short-term changes of dietary phosphate intake primarily affect abundance of NaPi-IIa protein, whereas changes in the abundance of NaPi-IIc and PiT-2 Na/Pi-cotransporters are slower (309) and likely occur by different mechanisms. For instance, although apical content of NaPi-IIc is reduced by high dietary phosphate, total cellular content was not altered, suggesting that the mechanism of regulation of NaPi-IIc is distinct from the NaPi-IIa cotransporter (265).Neither the nature nor the locus of possible phosphate signaling pathways that provoke proximal tubular adaptation of Na/Pi-cotransporters in response to changes in phosphate intake are known yet. Among the various candidates, PTH, calcitonin, vitamin D metabolites, thyroxine, growth hormone, FGF23, and, the pituitary gland have been discarded (34, 83). When directly introduced into the rat duodenum, phosphate elicited an increase of phosphate excretion within 15 min that was independent of altered serum levels of PTH, FGF23, serum phosphate concentration and was also not dependent on renal nerves (32, 161). Based on this data, a –yet unknown- intestinal endocrine factor (termed 'intestinal phosphatonin') was proposed that could participates in an intestine-renal signalling axis. However, it has also been shown, that contact with intestinal mucosa can be bypassed by intravenous injection of a phosphate bolus. Continuous infusion of phosphate into thyroparathyroidectomized rats adapted to low phosphate diet has been shown to down-regulate brush border membrane Na/Pi-cotransport within a short period of time (58). This suggests that serum concentration of phosphate may represent the signal for renal adaptation of Na/Pi-cotransport, and secondly that the signaling mechanisms may be intrinsic to the kidney itself (27).

SULFATE

Inorganic sulfate is taken up by diet and is critical for several basic processes such as forming very stable disulfide bonds within or between proteins (e.g. in keratins), forming part of enzymes or vitamins such as coenzyme A, thiamine and biotin, or being part of redox systems such as glutathione and thioredoxins. Sulfate plays an important role in detoxification by the liver, and for the structural integrity of bone and cartilage.

The main source of sulfate is dietary intake of protein comprised of sulfur-containing amino acids, mostly cysteine and methionine. Additional sources are water which may contain significant amounts of sulfate. Free inorganic sulfate is readily absorbed from diet in a Na^+-dependent process occurring mostly in the small intestine and is mediated by mechanisms and molecules similar if not identical to renal reabsorption of inorganic sulfate (see below) (97, 223). Daily intake of sulfate has been reported to be in the range of 0.2 to 1.5 g (2.1–15.8 mmol)/day (97).

Protein catabolism, mostly in liver, releases sulfate from cysteine and methionine containing proteins in parallel with elevated ureagenesis thereby correlating urinary sulfate and urea excretion (114, 133, 252). Urinary sulfate excretion may be even used as a marker of catabolism of sulfur-containing proteins (121, 131).

PLASMA SULFATE CONCENTRATION

In plasma, inorganic sulfate concentrations range between 0.2 and 1.1 mmol/l with an average of about 0.6 mmol/l (22). The main source of inorganic sulfate in the body is dietary uptake and metabolism of the sulfur containing amino acids cysteine, methionine, and to a lesser extent homocysteine and taurine.

In humans, low circulating sulfate levels are not associated with specific diseases, however, rare inborn disorders of organ and cell specific sulfate transporters have been reported to cause severe malformations such as diastrophic dysplasia, a disorder affecting primarily chondrocytes (127).

RENAL HANDLING OF SULFATE

Because SO_4^{2-} is freely filtered (113) the rate of urinary excretion is determined by the rate of reabsorption and secretion along the proximal tubule. Sulfate reabsorption is an active process, regulated, and saturable (182). With increasing intake, the filtered sulfate load exceeds the threshold for maximal tubular reabsorption and increasing amounts of sulfate appear in urine. Under normal dietary sulfate supply, the fractional excretion of sulfate is approximately 10 % in dog (113), whereas in rat the fractional excretion is around 30 % with plasma concentrations of sulfate of approximately 0.7 – 1 mmol/L (22, 159, 222).

The mechanisms by which sulfate is transported along the nephron have been thoroughly examined using micropuncture in vivo (67, 130, 296, 297, 298, 299, 300, 301, 302, 305), microperfusion of isolated tubules ex vivo (44), and isolation of vesicles of brush border and basolateral membranes (16, 116, 188, 189, 242, 260, 294). Several aspects have been reviewed recently (193, 200, 202, 203, 204).

Sulfate is actively transported in the proximal tubule across the luminal brush border membrane as well as via the basolateral membrane of cells (44, 67,189, 241, 260, 294, 296, 297, 298, 299, 300, 301, 302, 305). Collectively, many studies demonstrated using micropuncture, isolated brush border and basolateral membrane vesicles that sulfate transport occurs mostly by a Na^+-dependent transport process across the brush border membrane and by sulfate/anion exchange in the basolateral membrane (Figure 2).

Brush border membrane vesicle studies showed a Na^+-dependent transport process with an estimated affinity for sulfate of approximately 600 μM and for sodium with about 36 mM (260, 294). Because the Hill coefficient was close to 2 it was assumed that the transport process was electroneutral. Following the cloning of NaSi1 transport induced currents were demonstrated that are due to the cotransport of 3 Na^+ ions per sulfate (48). The luminal, Na^+-dependent transport process interacts with thiosulfate, selenate, chromate, and molybdate but not phosphate (67, 297).

The luminal membrane, however, has also an additional transport system mediating the exchange of intracellular sulfate for extracellular anions, most

likely bicarbonate and oxalate. Thereby the proximal tubule is able to secrete sulfate into urine (44, 81, 163, 242, 284). Whether the latter transport pathway characterized mostly in isolated brush border membrane vesicles has physiological relevance depends on the availability of intracellular and extracellular transport substrates. In mice lacking CFEX (possibly the molecular correlate of this transport activity) no sulfate related phenotype has been reported to date (see below).

In contrast, the basolateral transport process is mediated by an anion exchange mechanism releasing sulfate into the extracellular space in exchange for anions such as bicarbonate, oxalate or hydroxyl ions (44, 120, 162, 188). The transport mechanism is inhibited by the stilbene derivates DIDS and SITS, nonspecific inhibitors of various anion transport systems (16). Of note, the transport substrates and sensitivity of the luminal and basolateral sulfate exchangers are different suggesting that each transport systems are encoded by distinct genes.

MOLECULAR IDENTIFICATION OF RENAL SULFATE TRANSPORTERS

NaSi1 (SLC13A1)

NaSi1 (NaS1, SLC13A1) was first identified by expression cloning from a rat kidney cDNA library in Xenopus oocytes and shown to mediate Na^+-dependent uptake of sulfate (20, 196). Homologues from other species including mouse and man have been further identified (20, 168). The human gene consists of 15 exons and is localized on chromosome 7q31-7q32 (168). The NaSi1 protein consists of 595 amino acids and is predicted to form a protein with 13 transmembrane domains (20, 168).

Transport of sulfate by NaSi1 is electrogenic and kinetic analysis suggests that probably 3 Na^+ ions are cotransported with one SO_4^{2-} ion per transport cycle by NaSi1 (48). NaSi1 transports SO_4^{2-}, thiosulfates, and selenate with affinities in the range of 100-500 μM, respectively, and sodium with an apparent Km of about 20 mM (48, 196). Structural and phylogenetic features of NaSi1 have been reviewed in more detail elsewhere (200). NaSi1 is expressed predominantly in kidney and small intestine. There it

localizes to the apical brush border membrane of early proximal tubule cells and enterocytes of the small intestine and possibly also colon (20, 228). Weak expression may occur also in testis, adrenal glands and adipose tissue. In rat and mouse kidney, NaSi1 immunostaining is predominant in the proximal convoluted tubule (S1 and S2 segments) and weaker in the straight proximal tubule (S3 segment). NaSi1 staining is found in cortical and juxtamedullary nephrons (65, 187).

Deletion of NaSi1 in mice demonstrated that apical Na^+-dependent sulfate transport is completely accounted for by NaSi-1 and mice display a sulfate losing phenotype (hypersulfaturia) (69). Hyposulfatemia is the consequence of both urinary sulfate losses as well as impaired intestinal uptake. NaSi1 deficient mice have been a useful tool to study the physiological roles of sulfate and the consequences of hyposulfatemia as exemplified by reduced fertility, growth retardation, impaired hepatic detoxification of drugs, changes in hepatic lipid metabolism, and impairment of CNS functions (69, 70, 71, 72, 73, 76, 77, 173, 174). Thus, intestinal uptake and renal reabsorption of sulfate depend critically on the presence and activity of NaSi-1.

SAT1 (SLC26A1)

SAT1 (SLC26A1) belongs to the family of SLC26 anion exchangers (87,193,221). Several members of this family have been shown to transport sulfate, most notably SAT1 (38, 194, DSTS (SLC26A2) (127, 147) and CFEX /PAT1 (Chloride-formate exchanger/ putative anion transporter 1 (SLC26A6) (144), and SLC26A11 (311).

SAT1 was identified by expression cloning (38). The protein consists of 703 amino acids and has 12 putative transmembrane domains. When expressed in heterologous expression systems SAT1 mediates the transport of a variety of anions including sulfate, bicarbonate, and oxalate. Chloride may also be transported but with low affinity and efficiency (157). This transport activity is mediated by an obligatory exchange mechanism where intracellular substrate is exchanged for extracellular substrate. The transporter interacts also with probenecid, selenate, phenol red, tungstate and DIDS. Whether these

substances are only inhibitors or transport substrates has not been fully explored (38).

SAT1 mRNA has been detected in many organs including kidney, liver, small intestine, skeletal muscle and brain (38). In rodent kidney, SAT1 is localized to the basolateral membrane of the proximal tubule with more intense staining of proximal convoluted tubules (e.g. S1 and S2 segments) than straight proximal tubules (e.g. S3 segment) (146) paralleling the apical localization of NaSi1 in the same segments (187). The localization of SAT1 in human kidney has not been reported to date.

In vivo studies with sat1 deficient mice provided evidence for a primary defect in renal sulfate handling but not oxalate or bicarbonate (see below) suggesting that SAT1 serves mostly the transepithelial transport of sulfate (75). SAT1 KO mice show renal sulfate wasting and hyposulfatemia consistent with a major role of SAT1 in the release of sulfate from proximal tubule cells into the basolateral space. The physiological counter-ion is likely bicarbonate. Even though oxalate interacts with the transporter with a higher affinity, the very low concentrations measured in normal human subjects and animals (in the range of 1-5 μM) and the high concentrations of bicarbonate (approx. 25 mM) at the basolateral membrane favour exchange of intracellular sulfate for extracellular bicarbonate (or chloride) (157). Interestingly, sat1 deficient mice also developed oxalate kidney stones, reminiscent of slc26a6 deficient mice (see below). The mechanism causing oxalate stones has not been elucidated to date.

CFEX/PAT1 (SLC26A6)

CFEX (SLC26A6, also known as PAT1) is expressed in the proximal tubule of the kidney and the small intestine and localizes to the apical brush border membrane (152). CFEX mediates the exchange of various anions including chloride, bicarbonate, oxalate, and also sulfate (144). Considering physiological concentrations and distribution (luminal vs intracellular) of these anions, sulfate is not a major substrate in vivo and might be rather excreted

than reabsorbed by CFEX. Mice lacking CFEX (*Slc26a6*$^{-/-}$) have no apparent abnormality of sulfate homeostasis but develop massive hyperoxaluria and oxalate kidney stones (143).

REGULATION OF SULFATE EXCRETION

Dietary Adaptation to high and low Sulfate Intake

Adaptive mechanisms in the proximal tubule are of primary importance in the regulation of systemic sulfate homeostasis. These adaptive changes in renal sulfate reabsorption in response to dietary sulfate intake are similar to those demonstrated for phosphate and allow for constant plasma sulfate concentrations. Dietary sulfate deprivation results in a significant decline of the renal sulfate clearance and the urinary excretion rate of sulfate (26, 199, 226, 255). Clearance experiments in guinea pigs fed for 6-10 days with low-sulfate diet (0.13%) demonstrated 86-91% fractional sulfate reabsorption at normal plasma sulfate concentrations while animals on high-sulfate diet (0.13% supplemented with 300 mg/kg/day sodium sulfate) decreased renal sulfate excretion to 55-70% (226). Similarly, dietary sulfate deprivation in rats exhibited decreased urinary excretion rates and renal clearance values after 8 days of treatment while serum sulfate concentrations were unchanged. *In vitro* transport studies in brush border membrane (BBM) and basolateral membrane (BLM) vesicles isolated from rats stabilized on either low methionine or control diets for 7-9 days showed an increase of the V_{max} for BBM sodium dependent sulfate transport in animals on low methionine diet (26). In contrast, in BBM vesicles of *Nas1*-deficient mice sodium sulfate transport was reduced by 90% (69). Thus, the increase in renal BBM sodium/sulfate cotransport is a key mechanism in the adaptive response to tubular sulfate handling while tubular secretion, if any, is negligible in rats and humans. More recent studies confirmed these findings and shed light on the cellular mechanisms involved. Rats treated with low methionine diet (0% and 0.3%) were able to maintain normal serum sulfate levels and exhibited marked increases in NaSi-1 cotransporter mRNA and protein levels (255). Accordingly, urinary sulfate excretion rate and renal sulfate clearance were significantly decreased approaching zero. However, animals on 0%

methionine diet and normal serum sulfate levels were growth retarded with loss of muscle mass suggestive of maintained serum sulfate levels due to muscle catabolism. Animals fed with 0.3% methionine diet were able to maintain body and muscle weight indicating sufficient adaptive renal sulfate reabsorptive mechanisms. Animals on high methionine diet (2.46%) showed unchanged serum sulfate levels associated with lower NaSi-1 mRNA abundance (255). Another study from Markovich et al. highlighted the crucial role of NaSi-1 in regulation of plasma sulfate concentration by using different sulfate diets (199). High sulfate diet in rats resulted in a marked decrease of BBMV sodium/sulfate cotransport activity paralleled by a significant decrease in NaSi-1 mRNA and BBM protein abundance. Both studies from Markovich and Sagawa et al. concluded that NaSi-1 plays a major role in maintaining serum sulfate concentrations within the physiological range, even NaSi-1 alone may not be responsible for the raised sulfate excretion in animals on high sulfate diet suggestive of either similar absorptive mechanisms or additional secretory processes being involved. The regulation of Sat-1 (SLC26a1) and CFEX (SLC26a6) by dietary sulfate has not been explored to date.

Thyroid Hormone

Serum sulfate levels are decreased in hypothyroid patients and higher in hyperthyroid patients (283). Thyroid hormone (T_3, triiodothyronine) increases the maximum transport capacity for sodium/ sulfate cotransport in mouse renal BBM vesicles while serum sulfate concentrations were unchanged (286). The absence of an effect of T_3 on serum sulfate levels may be due to increased cellular uptake and utilization of sulfate, inhibition of renal sulfate reabsorption in the distal nephron, reduced intestinal sulfate absorption, or a combination of all. Similarly, experimental hypothroidism in rats decreases serum sulfate concentrations, lowers renal fractional reabsorption of sulfate and creatinine clearance. Sodium-dependent sulfate uptake into BBMV is reduced while K_m values are not different (257). In contrast, there were no significant differences in K_m and V_{max} for the sulfate/ anion exchange process in basolateral membrane vesicles. NaSi-1 mRNA and protein levels were

significantly reduced in hypothyroid rats indicating that hypothyroidism affects NaSi-1 mRNA and/or protein expression. The *Nas1* promoter region contains T_3 responsive elements (74).

Vitamin D_3

Renal sulfate reabsorption has been shown to be regulated by Vitamin D_3 status. Vitamin D-deficient rats develop hyposulfatemia, enhance fractional excretion of sulfate, and decrease renal sodium sulfate cotransport activity (93). The changes in sodium sulfate cotransport activity are caused by a decrease of V_{max} but not K_m of the transport system paralleled by reduction of both NaSi-1 cotransporter protein and mRNA levels. Vitamin D_3 supplementation corrects hyposulfatemia, normalizes fractional sulfate excretion, and normalizes NaSi-1 mRNA and protein levels. Most likely the active $1,25(OH)_2D_3$, but not plasma calcium nor PTH levels are responsible for the alterations of NaSi-1 expression and activity in this model. $1,25-(OH)_2D_3$ stimulates the transcriptional activation of the *Nas1* promoter. However, Sat-1 mRNA and protein levels in the kidney and liver are not altered by vitamin D_3 deficiency (21). Mice lacking the vitamin D receptor show a significant increase of urinary sulfate excretion by 40% paralleled by a fall in serum sulfate concentrations of 50% (39). NaSi-1 mRNA levels in the kidney are markedly decreased by 70% whereas intestinal NaSi-1 levels are not altered. The impact of vitamin D_3 on NaSi-1 expression and sulfate metabolism is independent of its effect on calcium metabolism, since similar results were observed in these animals after normalization of blood calcium levels. In addition, treatment of wild-type mice with vitamin D_3 increases renal NaSi-1 mRNA abundance. Taken together, the data provide evidence that vitamin D_3 plays a crucial role in sulfate regulation by affecting renal NaSi-1 expression.

Glucocorticoids

Glucocorticoids reduce renal sulfate reabsorption in rat, chicken and winter flounder (247,248,254). Systemic treatment with the glucocorticoid,

dexamethasone, decreased sodium dependent sulfate transport in chick renal BBM due to decreases in the maximum transport capacity V_{max} of ~ 50% without changes in K_m or any other sulfate transport processes in either BBM or BLM (247). Similar results have been obtained from the marine winter flounder when treated with dexamethasone. Transepithelial sulfate transport in flounder renal tubule primary monolayer cultures treated with hydrocortisone was significantly higher than in cortisol-free tissue (247). Further evidence for the role of glucocorticoids in regulation of renal sulfate transport was provided from experiments in adrenalectomized rats that were either treated with methylprednisolone (MPL) or vehicle. NaSi-1 mRNA and protein levels were reduced in kidney cortex of MPL-treated animals that was paralleled by a 2-fold increase in urinary sulfate excretion and almost 3-fold increase in renal sulfate clearance (254). Changes in NaSi-1 mRNA and protein expression were time-dependent. mRNA levels were significantly decreased after 4 and 6h after a single dose MPL. Protein expression was significantly diminished after 4, 6, and 12h after MPL administration. Accordingly, the V_{max} for sodium sulfate cotransport in the BBM was significantly decreased whereas the apparent K_m values or sulfate anion exchange in the BLM were unchanged in MPL-treated adrenalectomized rats (254). Finally, Beck and Markovich described the presence of five putative glucocorticoid responsive elements in the *Nas1* promoter region (20) suggesting that glucocorticoids in fact directly regulate *Nas1* gene transcription (202).

Growth Hormone/Ageing

Sulfate reabsorption by the kidney in young animals or humans is higher than in adult or aged individuals. In immature guinea pigs urinary sulfate excretion is low and and increases with aging (227). In young animals, low-sulfate diet did not appreciably stimulate V_{max} whereas a high-sulfate diet resulted in a decrease of V_{max} with no changes of K_m in any age group indicating that renal sulfate uptake responds to conditions with increased need of sulfate such as growth. In contrast, aged rats showed a higher sulfate excretion rate when compared to young animals without changes in serum sulfate concentrations

(15). Cell culture studies using Madin-Darby canine kidney (MDCK) cells stably transfected with NaSi-1 increased sodium sulfate cotransport after incubation with growth hormone (GH) and insulin-like growth factor I (IGF-I) (172). A recent study examined changes in NaSi-1 mRNA and protein levels in old rats (22-23 months old) and compared them with adult rats (9-10 months). Both NaSi-1 mRNA and protein abundance were significantly lower in the aged animals and transiently increased after treatment with growth hormone (256). The data suggest that aging in animals is associated with a decrease of NaSi-1 mRNA and protein expression due to lower GH concentrations.

Metabolic Acidosis

Changes of blood pH such as metabolic acidosis cause adaptive changes in the activity of several proximal tubule transport proteins such as the apical sodium proton exchanger, the vacuolar H^+-ATPase, and the basolateral sodium bicarbonate cotransporter (3, 56, 239). Children with classic renal tubular acidosis have significantly elevated renal sulfate excretion when compared to weight-matched controls (57). Similarly, in rats induction of metabolic acidosis increases significantly the fractional sulfate excretion (104). Puttaparthi et al. investigated the influence of metabolic acidosis on NaSi-1 cotransport activity, protein and mRNA expression (243). Acute acidosis (6-24h) and chronic (10 days) acidosis were induced in rats with NH_4Cl in drinking water and chow. Increased urinary sulfate excretion correlated with decreased sodium dependent sulfate cotransport activity in BBM vesicles of acidotic rats (2.4-fold). Accordingly, both cortical NaSi-1 mRNA abundance and BBM NaSi-1 protein expression were decreased by 2.8- and 2.2-fold, respectively. The reduction in sodium dependent sulfate cotransport activity was detectable after 24h, but not after 12h, of metabolic acidosis. The data suggest that decreased mRNA and protein abundance of NaSi-1 and reduced BBM NaSi-1 cotransport activity may play a crucial role in the inhibition of NaSi-1 activity by metabolic acidosis. In the marine teleost flounder acidosis similarly increases renal sulfate excretion (233). Primary cultures of the winter flounder renal proximal tubule epithelium were mounted in Ussing chambers

and metabolic acidosis mimicked by reducing the interstitial pH to 7.1 (normally 7.7). Sulfate net secretion in flounder proximal tubule cells was stimulated by 41% in metabolic acidosis when compared to paired isohydric controls and prevented by administration of the carbonic anhydrase inhibitor methazolamide. Also, administration of EIPA (a pyrazine-ring substituted amiloride derivative blocking NHE3 activity) to the lumen blocked this stimulation. Thus, carbonic anhydrase and BBM sodium proton exchanger activity may be required in this model for the acute stimulation of sulfate secretion by acidosis. In summary, metabolic acidosis reduces the expression of the major BBM sodium sulfate cotransporter NaSi-1 and thereby affects sulfate homeostasis.

Hypokalemia

Hypokalemia has been shown to modulate several proximal tubule transport proteins (178, 273). Rats that were treated for 7 days with a potassium-deficient diet had hyposulfatemia, increased fractional sulfate excretion, and a significant decrease of the BBM sodium/sulfate cotransport activity (201). The reduction in BBM sodium/sulfate cotransport activity was correlated with decreases in cortical NaSi-1 mRNA and BBM protein expression. Accordingly, Xenopus oocytes injected with mRNA from K^+-deficient rats showed a significant reduction in sodium sulfate cotransport but no changes in $_L$-leucine uptake suggesting that in low-K^+ diet down-regulation of NaSi-1 mRNA and protein is the potential underlying mechanism involved.

Pregnancy and postnatal Growth

As described above, during postnatal growth renal sulfate reabsorption is increased (170, 227, 234). In children an age-dependent curvilinear regression exists for serum sulfate concentrations showing highest serum sulfate levels at birth (0.47 mmol/l) which decrease constantly to 0.33 mmol/l during the following three years of life (60). In guinea pigs, the decrease in renal sulfate excretion with age was based on significantly decreased V_{max} values for sodium dependent sulfate cotransport in BBM while K_m values were not different (170). Using pregnant and non-pregnant animals V_{max} and K_m

values for BBM sulfate transport were significantly higher in pregnant animals. In contrast, sulfate anion exchange in BLM was unchanged among the different age groups. However, in pregnant guinea pigs K_m of the BLM sulfate transport was significantly higher while V_{max} was not different when compared to non-pregnant animals. A study looking at the ontogeny of renal sulfate transporter expression during postnatal maturation in 1 to 77 days old rats revealed that mRNA expression of both NaSi-1 and Sat-1 increase during the first 2 postnatal weeks (195). However, Sat-1 protein abundance increased in parallel while NaSi-1 protein levels remained steady. In conclusion, several studies indicate that sulfate is conserved in young and pregnant animals due to stimulated proximal tubule sulfate uptake as well as increased expression of both transporters involved in renal sulfate reabsorption, namely NaSi-1 and Sat-1, respectively. These changes may reflect conditions of increased need for sulfate substrates during growth and pregnancy.

Membrane Fluidity

The activity and kinetics of membrane transport proteins have been described to be affected by membrane fluidity. Sodium-dependent renal glucose and phosphate transport have been shown to be altered by changes in membrane fluidity (179, 280). In MDCK cells stably transfected with NaSi-1 preincubation with cholesterol significantly decreased the V_{max} for sodium dependent sulfate transport with no changes in K_m while addition of benzyl alcohol stimulated sulfate uptake by 20% (171). These changes correlated with decreased membrane fluidity, measured by the fluorescence polarization of 1,6-diphenyl 1,3,5-hexatriene (DPH), after incubation with cholesterol and increased membrane fluidity following administration of benzyl alcohol.

Non-steroidal anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti inflammatory drugs (NSAIDs) such as Indomethacin, Salicylic acid, Tiaprofenic acid, and Ibuprofen modulate renal sulfate clearance (24, 25, 66, 218, 219, 220, 253). Rats infused with Ibuprofen or Indomethacin demonstrated a markedly increased renal sulfate clearance (218). Many of these drugs affect prostaglandin synthesis. PGE2 alone does not alter renal sulfate clearance whereas PGE2 adminstration is able to

prevent the effects of Ibuprofen or Indomethacin on renal sulfate clearance. Moreover, Indomethacin, Ibuprofen, and Tiaprofenic acid may directly affect renal sulfate transport in rat kidney BBM and BLM vesicles (24). The effects of Ibuprofen on basolateral sulfate transport are controversial. Treatment of rats resulted in a decrease of the sodium-dependent sulfate cotransport capacity in BBM vesicles with unchanged K_m. In contrast, BLM sulfate transport was not affected. The decreased BBM sulfate transport was paralleled by a significant down-regulation of NaSi-1 mRNA and protein expression (253). Among all three NSAIDs, Indomethacin has the strongest inhibitory effect on renal sulfate handling. Also effects of Salicylic acid on renal sulfate transport are controversial. Direct incubation of BBM and BLM vesicles demonstrated significantly lower transport of sulfate whereby the K_i of Salicylic acid was much lower for BLM transport (66). However, part of these data is in contrast to previous studies where Salicylic acid did not inhibit sulfate transport across the BLM in micropuncture studies (301). Thus, NSAID affect renal sulfate transport, but the mechanim(s) underlying this effect have not been clarified.

Chronic renal Failure

Hypersulfatemia as well as hyperphosphatemia are present in patients with chronic renal failure (101, 212, 213, 214, 283). In patients on maintenance hemodialysis an eight-fold increase of plasma sulfate concentrations is observed (192). Similar observations were made in children with chronic kidney disease (212). Here, plasma sulfate concentrations were inversely correlated with glomerular filtration rate and highest in children treated with regular dialysis. In rats with experimental chronic renal failure (subtotal nephrectomy), hypersulfatemia was detectable as early as three weeks after subtotal nephrectomy, rose further after six weeks and was paralleled by twofold increase of fractional renal sulfate excretion (94). In these kidneys, NaSi-1 and Sat-1 total protein expression was decreased due to loss of functional kidney tissue while relative NaSi-1 cotransporter abundance was increased. Also hypersulfatemia despite of increased renal sulfate excretion could not be clearly explained. Human studies suggest a role for hypersulfatemia in the development of hyperparathyroidism (214). Patients with chronic renal failure demonstrated a positive correlation between plasma

sulfate and serum creatinine concentrations. In contrast, ionized calcium was inversely correlated with phosphate but also sulfate and parathyroid hormone. Calcium is able to bind sulfate and build calcium sulfate complexes. The resultant fall of ionized calcium might stimulate parathyroid hormone secretion by the parathyroid glands. Accordingly, in children on hemodialysis hyperparathyroidism occurs with even normal calcium levels (211). Taken together, hypersulfatemia in chronic renal failure might play a role in the development of secondary hyperparathyroidism and renal osteodystrophy by aggravating complex formation with calcium.

Heavy Metals

Heavy metal intoxication can result in a generalized dysfunction of the proximal tubule including proteinuria, glucosuria, phosphaturia, and sulfaturia (128, 215, 237, 307). The effect of several heavy metals on both renal sulfate transport proteins, NaSi-1 and Sat-1, respectively was examined (197, 198). Mercury strongly inhibited sodium dependent sulfate cotransport in Xenopus oocytes by decreasing both V_{max} and K_m of sulfate transport by NaSi-1 (197). Lead also markedly inhibited NaSi-1 mediated sulfate uptake, however, only V_{max} was decreased while K_m was unchanged. In contrast to Mercury, this inhibition was fully reversible. Compared to Mercury and Lead, Cadmium contributed to a small decrease in V_{max} and thus to a weak inhibition of NaSi-1 transport, which was fully reversible similar to lead. Of note, a previous study performed in rats demonstrated no changes in sulfate uptake in Cadmium-treated animals (128). Similar to mercury, chromium also inhibited NaSi-1 by decreasing both V_{max} and K_m of sulfate transport by approximately 7-fold which was again fully reversible. Similar to NaSi-1, the activity of the sulfate transporter Sat-1 was also inhibited by the heavy metals mercury, lead, cadmium, and chromium (197). Mercury inhibited Sat-1 mediated sulfate transport in Xenopus oocytes by reduction of V_{max} by 8-fold with no changes of K_m and was similar to NaSi-1 not reversible by simple washout. In contrast to NaSi-1, lead did not affect Sat-1 mediated sulfate uptake. Relatively high millimolar concentrations of cadmium were needed to induce significant inhibition of sulfate uptake by reducing V_{max} but not K_m. Chromium only affected K_m but not V_{max} of Sat-1 sulfate uptake.

Figure legends

Figure 1: Model of a proximal tubule cell depicting transport pathways of phosphate across the luminal and basolateral membrane. On the luminal brush border membrane at least three transporters exist that can mediate sodium-dependent phosphate transport. The Na^+-dependent uptake of phosphate from primary urine is mediated by NaPi-lla, NaPi-llc and PiT-2. The relative contribution of these three phosphate transporters may differ among different species. These transporters are energized by the membrane potential and Na^+ gradient generated by basolateral Na^+/K^+-ATPases. Phosphate exits proximal tubular cells across the basolateral membrane by a yet unknown transport pathway.

Figure 2

Model of a proximal tubule cell (early proximal tubule) depicting transport pathways of sulfate across the luminal and basolateral membrane. On the luminal brush border membrane at least two transporters exist that can mediate sulfate transport. The Na^+-dependent uptake of sulfate from primary urine is mediated by the NaSi sulfate transporter. This transporter is energized by the membrane potential and Na^+ gradient generated by basolateral Na^+,K^+-ATPases. Sulfate may also be excreted into primary urine by an anion exchanger, most likely CFEX, that transports sulfate in exchange for oxalate, chloride or bicarbonate. This transport pathway is also linked to Na^+-H^+-exchange mediated mostly by NHE3. Sulfate exits proximal tubular cells across the basolateral membrane in exchange for extracellular anions through the SAT1 anion exchanger. Intracellular bicarbonate is excreted into the basolateral space by the NBCe1 electrogenic Na^+-HCO_3^- -cotransporter. Also this transport process is linked to the NHE3 transporter and carbonic anhydrases generating bicarbonate.

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